Decline of a visceral leishmaniasis epidemic in HIV-infected patients after the introduction of highly active antiretroviral therapy (HAART)

Leishmania infantum causes endemic visceral leishmaniasis (VL) in the Mediterranean basin. A progressive increase in the number of cases of VL has been observed in southern Europe since the mid-1980s. VL is considered an emerging opportunistic disease, mainly due to the HIV pandemic: between 25 and 75% of cases of adult VL occur in HIV-positive patients and 2–9% of AIDS patients suffered VL [1,2]. These figures were obtained at a time when doctors had only a handful of weak drugs to treat HIV infection. Since the introduction of protease inhibitor (PI)-containing regimens, an increase in survival rates and a decline in the number of HIV-associated opportunistic infections have been observed [3]. However, very few data are available concerning the effect of PI on *Leishmania*–HIV co-infected patients.

The objective of this study was to determine if the introduction of highly active antiretroviral therapy (HAART) with PI-containing regimens was able to reduce the number of new VL cases in HIV-infected patients. The study was performed at the Ramón y Cajal Hospital (Madrid, Spain), a public hospital with 1100 beds, serving a well defined area in northern Madrid (officially called Area 4). This hospital is the only source of tertiary level care for the 550 000 population living in that area.

From 1987 to 1999, HIV-infected patients diagnosed with a first episode of VL were recorded. Most HIV-infected patients were evaluated every 3 months, or more frequently if necessary. An active search for *Leishmania* was conducted in all patients with prolonged fever and/or visceromegalies and/or cytopenias. Diagnosis of VL was accepted only if (i) there was a compatible clinical illness; (ii) there was parasitologic confirmation by demonstration of *Leishmania* amastigotes in Giemsa-stained smears; (iii) promastigotes were isolated in parasitic culture (NNN medium) obtained from aspirates of spleen, lymph node, blood, liver or bone marrow. No search for the parasite was carried out in asymptomatic patients. CD4+ count was measured by flow cytometry. HIV RNA levels were determined by an ultrasensitive method with a lower limit of detection of 50 copies/mL (Chiron Diagnostics, Emeryville, CA, USA). During follow-up, antiretroviral treatment change was decided by the clinician caring for the patient, according to published guidelines.

Pre-HAART era: From 1987 to 1996 (a 120-month study period), a total of 72 newly diagnosed cases of VL were recorded. At the time of their first episode of VL, 42.3% patients met the European diagnostic criteria for AIDS, but most patients were strongly immunocompromised (mean CD4+ = 47 cells/μL). Clinico-epidemiological characteristics, survival and prognostic factors of those patients have been published previously [4].

HAART era: PI was started on some patients in 1996, but the majority of HIV-infected patients received PI from January 1997, the point at which the second phase of the study was started, until December 1999 (36 months). A first episode of VL after starting HAART (average time 22 months, range 6–26) was recorded in three patients. All of these patients were non-responders (failure of the antiretroviral drugs). When VL was diagnosed, they had an average CD4+ count of 82 cells/mm^3 (range 30–144) and viral load of 5.9 log (range 5.8–6 log).

There was a decrease in the incidence of new VL cases during HAART (3/375; 0.8 new VL cases per 100 AIDS cases; i.e. 0.26 new VL cases per 100 AIDS person/years) compared with the pre-HAART era (72/1479; 4.81 new VL cases per 100 AIDS cases, i.e. 0.48 new VL cases per 100 AIDS person/years) was observed ($P < 0.0005$). The occurrence of new VL cases before and after HAART is shown in Table 1.

The benefit of HAART in reducing the incidence of nearly all AIDS-defining opportunistic infections is well known, but very few data are presently available on the effect of HAART on leishmaniasis. The results obtained point out a significant decrease in the incidence of new VL cases in HIV-infected patients after the introduction of HAART. These results are in accordance with other studies carried out in Rome, Italy (a decrease from 0.7 cases per 100 person/years to 0.13 cases per 100 person/years) [5], in Barcelona, Spain (a decrease from 0.8 cases per 100 person/years to 0.12 cases per 100 person/years) [6], and in Seville, Spain (a decrease from 1.9 cases per 100 persons/2 years to 0.3 cases per 100 persons/2 years) [7]. No controls were included in any of these studies and the decrease of VL–HIV cases could be coincidental, as *Leishmania* could be transmitted by sharing syringes among intravenous drug users. A decrease in new VL cases could be attributed to the introduction of syringe exchange programs or other alternative hypotheses besides the antiretroviral treatment.

On the other hand, it is not yet clear if HAART is able to reduce VL recurrence in HIV-infected patients with a previous VL episode. Some studies have found little, if any, benefit to receiving HAART, even if an undetectable viral load and marked CD4+ increase above 200 cells/μL was achieved, and prevented a relapse in the VL–HIV co-infected [8,9].

VL is controlled by cellular immunity, and TH1 response results in host protective immunity to *Leishmania*. HIV and *Leishmania* multiply their effects if they occur concurrently, switching from TH1 to TH2 CD4+ response. HAART could be strong enough to inhibit viral replication but not to switch from TH2 to TH1 response in some patients. In addition to this, other factors (such as parasite virulence, parasitic load, individual susceptibility, host parasitic immunity before HIV infection) may play a role in explaining the differences in the host immune response and clinical evolution observed among patients [10].

Table 1 Occurrence of new cases of visceral leishmaniasis before and after starting highly active antiretroviral therapy (HAART) including protease inhibitor-containing regimens

	Pre-HAART era	HAART era	*P*-value
Interval	1987–96 (120 months)	1997–99 (36 months)	
HIV therapy	NRTIs	HAART	
AIDS new cases	1497	375	
VL-new cases	72	3	
VL-new cases per 100 AIDS cases	4.81 (95% CI = 3.84–6.01)	0.80 (95% CI = 0.27–2.33)	< 0.0005

NRTIs, nucleoside reverse-transcriptase inhibitors; HAART, highly active antiretroviral therapy with protease inhibitor-containing regimens; VL, visceral leishmaniasis; AIDS, acquired immunodeficiency syndrome; 95% CI, 95% confidence interval.

Although the number of patients in our study is small, the results indicate that HAART decreases the incidence of new cases of VL and that this opportunistic parasitic disease appears only when there is evidence of HAART failure. In our study, the only three new cases of VL after 1997 were non-responders to HAART therapy.

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